Acute vs. Chronic Pain

What is pain?
Pain is an uncomfortable feeling and/or an unpleasant sensation in the body. The presence of **pain** often is an indication that something is wrong. **Pain** can appear suddenly or can come about slowly.

Each individual is the best judge of his or her own **pain**. Feelings of **pain** can range from mild and occasional to severe and constant. **Pain** can be classified as **acute pain** or **chronic pain**.

What is acute pain?
Acute pain begins suddenly and is usually sharp in quality. It serves as a warning of disease or a threat to the body. **Acute pain** might be caused by many events or circumstances, including:

- Surgery
- Broken bones
- Dental work
- Burns or cuts
- Labor and childbirth

Acute pain might be mild and last just a moment, or it might be severe and last for weeks or months. In most cases, **acute pain** does not last longer than six months, and it disappears when the underlying cause of **pain** has been treated or has healed. Unrelieved **acute pain**, however, might lead to **chronic pain**.

What is chronic pain?
Chronic pain persists despite the fact that the injury has healed. **Pain** signals remain active in the nervous system for weeks, months, or years. Physical effects include tense muscles, limited mobility, a lack of energy, and changes in appetite. Emotional effects include

depression, anger, anxiety, and fear of re-injury. Such a fear might hinder a person's ability to return to normal work or leisure activities. Common **chronic pain** complaints include:

- Headache
- Low back **pain**
- Cancer **pain**
- Arthritis **pain**
- Neurogenic **pain** (**pain** resulting from damage to nerves)
- Psychogenic **pain** (**pain** not due to past disease or injury or any visible sign of damage inside)

Chronic pain might have originated with an initial trauma/injury or infection, or there might be an ongoing cause of **pain**. However, some people suffer **chronic pain** in the absence of any past injury or evidence of body damage.

What is the difference between acute and chronic pain?

- There might be no known **cure** for the disease (such as arthritis or phantom **pain**) that is causing the **chronic pain**.
- The cause of **chronic pain** might be unknown or poorly understood.

How is pain treated?
Depending upon its severity, **pain** might be treated in a number of ways. Symptomatic options for the treatment of **pain** might include one or more of the following:

- Non-steroidal anti-inflammatory drugs (NSAIDs), a specific type of painkiller such as Motrin or Aleve
- Acetaminophen (such as Tylenol)
- Narcotics (such as morphine or codeine)
- Localized anesthetic (a shot of a **pain** killer medicine into the area of the **pain**)
- Nerve blocks (the blocking of a group of nerves with local anesthetics)
- Acupuncture
- Electrical stimulation
- Physical therapy
- Surgery
- Psychotherapy (talk therapy)
- Relaxation techniques such as deep breathing
- Biofeedback (treatment technique in which people are trained to improve their health by using signals from their own bodies)
- Behavior modification

Some **pain** medicines are more effective in fighting **pain** when they are combined with other methods of treatment. Patients might need to try various methods to maintain maximum **pain** relief.

Click here to go to the **Pain** Management Department Web site.

Know someone who could use this information?....send them this link.

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Pain Management: Complex Regional Pain Syndrome

Complex regional **pain** syndrome (CRPS), also called reflex sympathetic dystrophy syndrome, is a chronic **pain** condition in which high levels of nerve impulses are sent to an affected site. Experts believe that CRPS occurs as a result of dysfunction in the central or peripheral nervous systems.

CRPS is most common in people aged 20-35. The syndrome also can occur in children; it affects women more often than men.

There is **no cure** for CRPS.

What Causes Complex Regional Pain Syndrome?

CRPS most likely does not have a single cause but rather results from multiple causes that produce similar symptoms. Some theories suggest that **pain** receptors in the affected part of the body become responsive

Get the Facts

Types of Pain

- Arachnoiditis
- Arthritis
- Rheumatoid Arthritis
- Osteoarthritis
- Burn **Pain**
- Cancer **Pain**
- Facial **Pain**
- Fibromyalgia
- Headaches
- Tension Headaches
- Cluster Headaches
- Migraine Headaches
- Spinal Headaches
- Musculoskeletal **Pain**
- Back **Pain**
- Neck and Shoulder **Pain**
- Whiplash
- Myofascial **Pain** Syndrome
- Neuropathic **Pain**
- Complex **Pain** Syndrome
- Central **Pain** Syndrome
- Postherpetic Neuralgia
- Phantom Limb **Pain**
- Diabetic Neuropathy
- Pelvic **Pain**
- Psychogenic **Pain**
- Sciatica
- Skin Disorders
- Shingles
- Herpes
- Skin Tumor & Cysts
- Scleroderma
- Neurofibromatosis
- Vasculitis
- Spasticity
- Spinal Cord Injury
- Sickle Cell Disease

to catecholamines, a group of nervous system messengers. In cases of injury-related CRPS, the syndrome may be caused by a triggering of the immune response which may lead to the inflammatory symptoms of redness, warmth, and swelling in the affected area. For this reason, it is believed that CRPS may represent a disruption of the healing process.

- Spinal Stenosis
- Spondylolithesis
- Temporomandibular Disorders
- Vascular Disease

Tests You Take

Treatments

Special Populations

Day-to-Day

Bookshelf

» To **Pain** Management Health Center

What Are the Symptoms of Complex Regional Pain Syndrome?

The symptoms of CRPS vary in their severity and length. One symptom of CRPS is continuous, intense **pain** that gets worse rather than better over time. If CRPS occurs after an injury, it may seem out of proportion to the severity of the injury. Even in cases involving an injury only to a finger or toe, **pain** can spread to include the entire arm or leg. In some cases, **pain** can even travel to the opposite extremity. Other symptoms of CRPS include:

- "Burning" **pain**
- Swelling and stiffness in affected joints
- Motor disability, with decreased ability to move the affected body part
- Changes in nail and hair growth patterns. There may be rapid hair growth or **no** hair growth.
- Skin changes. CRPS involves changes in skin temperature – skin on one extremity can feel warmer or cooler compared to the opposite extremity. Skin color changes also are apparent as the skin is often blotchy, pale, purple or red. The texture of skin also can change, becoming shiny and thin. People with syndrome may have skin that sometimes is excessively sweaty.

CRPS may be heightened by emotional stress.

How Is Complex Regional Pain Syndrome Diagnosed?

There is **no** specific diagnostic test for CRPS, but some testing can rule out other conditions. Triple-phase bone scans can be used to identify changes in the bone and in blood circulation. Some health care providers may apply a stimulus (for example, heat, touch, cold) to determine whether there is **pain** in a specific area.

Making a firm diagnosis of CRPS may be difficult early in the course of the disorder when symptoms are few or mild. CRPS is diagnosed primarily through observation of the following symptoms:

- The presence of an initial injury
- A higher-than-expected amount of **pain** from an injury
- A change in appearance of an affected area
- The presence of **no** other cause of **pain** or altered appearance

How Is Complex Regional Pain Syndrome Treated?

Since there is **no cure** for CRPS, the goal of treatment is to relieve painful symptoms associated with the disorder. Therapies used include psychotherapy, physical therapy, and drug treatment, such as topical analgesics, narcotics, corticosteroids, antidepressants and anti-seizure drugs.

Other treatments include:

- **Sympathetic nerve blocks:** These blocks, which are done in a variety of ways, can provide significant **pain** relief for some people. One kind of block involves placing an anesthetic next to the spine to directly block the sympathetic nerves.
- **Surgical sympathectomy:** This controversial technique destroys the nerves involved in CRPS. Some experts believe it has a favorable outcome, while others feel it makes CRPS worse. The technique should be considered only for people whose **pain** is dramatically but temporarily relieved by selective sympathetic blocks.
- **Intrathecal drug pumps:** Pumps and implanted catheters are used to send **pain**-relieving medication into the spinal fluid.
- **Spinal cord stimulation:** This technique, in which electrodes are placed next to the spinal cord, offers relief for many people with the condition.

Get tips on how to better cope with chronic **pain.**
View the full table of contents for the **Pain** Management Guide.

Reviewed by the doctors at The Cleveland Clinic **Pain** Management Department.

Edited by Charlotte E. Grayson, MD, WebMD, June 2004.

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Protein kinase

From Wikipedia, the free encyclopedia

A **protein kinase** is an enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). This usually results in a functional change of the target **protein** (substrate) by changing enzyme activity, cellular location, or association with other proteins. Up to 30% of all proteins may be modified by **kinase** activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction, the transmission of signals within the cell. The human genome contains about 500 **protein kinase** genes; they constitute about 2% of all eukaryotic genes.

The chemical activity of a **kinase** involves removing a phosphate group from ATP and covalently attaching it to one of three amino acids that have a free hydroxyl group. Most kinases act on both serine and threonine, others act on tyrosine, and a number (dual specificity kinases) act on all three.

Because **protein** kinases have profound effects on a cell, their activity is highly regulated. Kinases are turned on or off by phosphorylation (sometimes by the **kinase** itself - *cis*-phosphorylation/autophosphorylation), by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates.

Disregulated **kinase** activity is a frequent cause of disease, particularly cancer, where kinases regulate many aspects that control cell growth, movement and death. Drugs which inhibit specific kinases are being developed to treat several diseases, and some are currently in clinical use, including Gleevec (imatinib) and Iressa (gefitinib).

Contents

Serine/threonine-specific protein kinases

Serine/threonine **protein** kinases (EC 2.7.11.1 (http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.1)) phosphorylate the OH group of serine or threonine (which have similar sidechains). Activity of these **protein** kinases can be regulated by specific events (e.g. DNA damage), as well as numerous chemical signals, including:

- **cAMP**/cGMP
- Diacylglycerol
- Ca^{2+}/calmodulin

While serine/threonine kinases all phosphorylate serine or threonine residues in their substrates, they select specific residues to phosphorylate on the basis of residues that flank the phosphoacceptor site, which together comprise the *consensus sequence*. Since the consensus sequence residues of the substrate to be phosphorylated make contact with the catalytic cleft of the **kinase** at several key amino acids (usually through hydrophobic forces and ionic bonds), a **kinase** is usually not specific to a single substrate, but instead can phosphorylate a whole "substrate family" having common recognition sequences. While the catalytic domain of these kinases is highly conserved, the sequence variation that is observed in the kinome (the subset of genes in the genome that encode kinases) provides for recognition of distinct substrates. Most kinases are inhibited by a pseudosubstrate that binds to the **kinase** like a real substrate but lacks the amino acid to be phosphorylated. When the pseudosubstrate is removed, the **kinase** can perform its normal function.

Many serine/threonine **protein** kinases do not have their own individual EC numbers and use "2.7.11.1". These were formerly included in EC number "2.7.1.37", which was a general EC number for any enzyme that phosphorylates proteins while converting ATP to ADP (i.e. ATP:**protein** phosphotransferases.) This category is currently being reviewed by the Nomenclature Committee of IUBMB (NC-IUBMB), and it is believed that the various serine/threonine-kinases will get their own EC numbers eventually.

Pelle is a serine/threonine **kinase** that can phosphorylate itself, and also Tube and Toll.

Phosphorylase kinase

Phosphorylase **kinase** (EC 2.7.11.19 (http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.19)) was in fact, the first Ser/Thr **protein kinase** to be discovered (in 1959 by Krebs *et al.*).

Protein kinase A

Protein kinase A (EC 2.7.11.1 (http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.1)) consists of two domains, a small domain with several β sheet structures and a larger domain containing several α helices. The binding sites for substrate and ATP are located in the catalytic cleft between the domains (or lobes). When ATP and substrate bind, the two lobes rotate so that the terminal phosphate group of the ATP and the target amino acid of the substrate move into the correct positions for the catalytic reaction to take place.

Regulation

Protein kinase A has several functions in the cell, including regulation of glycogen, sugar, and lipid metabolism. It is controlled by **cAMP**: in the absence of **cAMP**, the **kinase** is a tetramer of two regulatory and two catalytic subunits (R_2C_2), with the regulatory subunits blocking the catalytic center of the catalytic subunits. Binding of **cAMP** to the regulatory subunit leads to dissociation of active RC dimers. Also, the catalytic subunit itself can be regulated by phosphorylation.

Downregulation of **protein kinase** A occurs by a feedback mechanism: one of the substrates that is activated by the **kinase** is a phosphodiesterase, which converts **cAMP** to AMP, thus reducing the amount of **cAMP** that can activate **protein kinase** A.

Protein Kinase B

Protein Kinase B is also known as AKT **kinase**. The v-akt gene was identified as the oncogene of retrovirus AKT8. The gene codes for a **protein kinase**. Human homologs of the AKT8 oncogenic **protein** were identifed in 1987.By 1995 it had been found that Akt kinases function as mitogen-activated kinases downstream from cell surface receptors that activate phosphoinositide 3-**kinase**. Three human akt genes exist. All three Akt kinases regulate cell proliferation and Akt2 is particularly important for insulin actions in cells. A major target of Akt kinases is glycogen synthase **kinase**-3.

Protein kinase C

Protein kinase C ('PKC', EC 2.7.11.1 (http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.1)) is actually a family of **protein** kinases consisting of ~10 isozymes. They are divided into three subfamilies: conventional (or classical), novel, and atypical based on their second messenger requirements. Conventional (c)PKCs contain the isoforms α, β_I, β_{II}, and γ. These require Ca^{2+}, diacylglycerol (DAG), and a phospholipid such as phosphatidylcholine for activation. Novel (n)PKCs include the δ, ε, η, and θ isoforms, and require DAG, but do not require Ca^{2+} for activation. Thus, conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase **C**. On the other hand, Atypical (a)PKCs (including ζ and ι / λ isoforms) require neither Ca^{2+} nor diacylglycerol for activation. The term "**protein kinase C**" usually refers to the entire family of isoforms.

Structure and regulation

The structure of all PKCs consists of a regulatory domain and a catalytic domain tethered together by a hinge region. The catalytic region is highly homologous among the different isoforms, as well as to a lesser degree the catalytic region of other serine/threonine kinases. The second messenger requirement differences in the isoforms are a result of the regulatory region, which are similar within the classes, but differ among them. Most of the crystal structure of the catalytic region of PKC has not been determined, except for PKC theta and iota. Due to its similarity to other kinases whose crystal structure have been determined, the structure can be strongly predicted.

The regulatory domain or the amino-teminus of the PKCs contains several shared subregions. The C1 domain, present in all of the isoforms of PKC has a binding site for DAG as well as non-hydrolysable, non-physiological analogues called phorbol esters. This domain is functional and capable of binding DAG in both conventional and novel isoforms, however, the C1 domain in atypical PKCs is incapable of binding to DAG or phorbol esters. The C2 domain acts as a Ca2+ sensor and is present in both conventional and novel isoforms, but functional as a Ca2+ sensor only in the conventional. The pseudosubstrate region, which is present in all three classes of PKC, is a small sequence of amino acids that mimic a substrate and bind the substrate-binding cavity in the catalytic domain keeping the enzyme inactive. When Ca2+ and DAG are present in sufficient concentrations, they bind to the C2 and C1 domain, respectively, and recruit PKC to the membrane. This interaction with the membrane results in release of the pseudosubstrate from the catalytic site and activation of the enzyme. In order for these allosteric interactions to occur, however, PKC must first be properly folded and in the correct conformation permissive for catalytic action. This is contingent upon phosphorylation of the catalytic region, discussed below.

The catalytic region or **kinase** core of the PKA, PKB (also known as Akt)and PKC kinases contains approximately 40% amino acid sequence similarity. This similarity increases to ~ 70% across PKCs and even higher when comparing within classes. For example, the two atypical PKC isoforms, ζ and ι/λ, are 84% identical (Selbie et al., 1993). Of the over 30 **protein kinase** structures whose crystal structure has been revealed, all of them have the same basic organization. They are a bilobal structure with a β sheet comprising the N-terminal lobe and an α helix constituting the C-terminal lobe. Both the ATP- and substrate-binding sites are located in the cleft formed by these two lobes. This is also where the pseudosubstrate domain of the regulatory region binds. Another feature of the PKC catalytic region that is essential to the viability of the **kinase** is its phosphorylation. The catalytic and novel PKCs have three phosphorylation sites, termed: the activation loop, the turn motif, and the hydrophobic motif. The atypical PKCs are phosphorylated only on the activation loop and the turn motif. Phosphorylation of the hydrophobic motif is rendered unnecessary by the presence of a glutamic acid in place of a serine, which, as a negative charge, acts similarly to a

phosphorylated residue. These phosphorylation events are essential for the activity of the enzyme, and 3-phosphoinositide-dependent **protein kinase**-1 (PDK1) is the upstream **kinase** responsible for initiating the process by transphosphorylation of the activation loop.(Balendran et al., 2000)

Upon activation, **protein kinase C** enzymes are translocated to the plasma membrane by RACK proteins (membrane-bound receptor for activated **protein kinase C** proteins). The **protein kinase C** enzymes are known for their long-term activation: they remain activated after the original activation signal or the Ca^{2+}-wave is gone. This is presumably achieved by the production of diacylglycerol from phosphatidylcholine by a phospholipase; fatty acids may also play a role in long-term activation.

Function

The consensus sequence of **protein kinase C** enzymes is similar to that of **protein kinase** A, since it contains basic amino acids close to the Ser/Thr to be phosphorylated. Their substrates are MARCKS proteins, MAP **kinase**, transcription factor inhibitor IκB, the vitamin D_3 receptor VDR, Raf **kinase**, calpain, and the epidermal growth factor receptor.

Ca^{2+}/calmodulin-dependent protein kinases

Also called *CaM kinases* (EC 2.7.11.17 (http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.11.17)), these kinases are primarily regulated by the Ca^{2+}/calmodulin complex. These kinases show a memory effect on activation. Two types of CaM kinases are:

- *Specialized CaM kinases*. An example is the myosin light chain **kinase** (MLCK) that phosphorylates myosin, causing muscles to contract.
- *Multifunctional CaM kinases*. Also collectively called *CaM **kinase** II*, which play a role in many processes, such as neurotransmitter secretion, transcription factor regulation, and glycogen metabolism. Between 1% and 2% of the proteins in the brain are CaM **kinase** II.

Structure and autoregulation

The CaM kinases consist of an N-terminal catalytic domain, a regulatory domain, and an association domain. In the absence of Ca^{2+}/calmodulin, the catalytic domain is autoinhibited by the regulatory domain, which contains a pseudosubstrate sequence. Several CaM kinases aggregate into a homooligomer or heterooligomer. Upon activation by Ca^{2+}/calmodulin, the activated CaM kinases autophosphorylate each other in an intermolecular reaction. This has two effects:

1. An increase in affinity for the calmodulin complex, prolonging the time the **kinase** is active.
2. Continued activation of the phosphorylated **kinase** complex even after the calmodulin complex has dissociated from the **kinase** complex, which prolongs the active state even more.

MAP kinases

Mitogen-activated **protein** kinases (MAPKs) (EC 2.7.11.1) respond to extracellular stimuli (mitogens) and regulate various cellular activities, such as gene expression, mitosis, differentiation, and cell survival/apoptosis. Extracellular stimuli lead to activation of a MAPK via a signaling cascade composed of MAPK, MAPK **kinase** (MAPKK), and MAPKK **kinase** (MAPKKK). A MAPKKK that is activated by extracellular stimuli phosphorylates a MAPKK on its serine and threonine residues, and then this MAPKK activates a MAPK through phosphorylation on its serine and tyrosine residues. This MAPK signaling cascade has been evolutionarily well-conserved from yeast to mammals.

To date, four distinct groups of MAPKs have been characterized in mammals: (1) extracellular signal-regulated kinases (ERKs), (2) c-Jun N-terminal kinases (JNKs), (3) p38 isoforms, and (4) ERK5. The ERKs (also known as classical MAPKs) signaling pathway is preferentially activated in response to growth factors and phorbol ester (a tumor promoter), and regulates cell proliferation and cell differentiation. The JNKs (also known as stress-activated **protein** kinases; SAPKs) and p38 signaling pathways are responsive to stress stimuli, such as cytokines, ultraviolet irradiation, heat shock, and osmotic shock, and are involved in cell differentiation and apoptosis. And ERK5, which has been found recently, is activated both by growth factors and by stress stimuli, and it participates in cell proliferation.

Mos/Raf kinases

Mos/Raf kinases form part of the MAPKK **Kinase** family and are activated by growth factors. The enzyme functions to stimulate growth of cells. Raf inhibition has become the target for new anti-metastatic cancer drugs as they inhibit the MAPK cascade and reduce cell proliferation.

Tyrosine-specific protein kinases

*Main article: Tyrosine **kinase***

Tyrosine-specific **protein** kinases (EC 2.7.10.1 (http://www.expasy.org/cgi-bin/nicezyme.pl?2.7.10.1)) phosphorylate tyrosine amino acid residues, and are, like serine/threonine-specific kinases, used in signal transduction. They act primarily as growth factor receptors and in downstream signaling from growth factors; some examples:

- Platelet-derived growth factor (PDGF) receptor;
- Epidermal growth factor (EGF) receptor;
- Insulin receptor and insulin-like growth factor (IGF1) receptor;
- Stem cell factor (*scf*) receptor (also called *c-kit*, see the article on gastrointestinal stromal tumor).

Receptor tyrosine kinases

These kinases consist of a transmembrane receptor with a tyrosine **kinase** domain protruding into the cytoplasm. They play an important role in regulating cell division, cellular differentiation, and morphogenesis. More than 50 receptor tyrosine kinases are known in mammals.

Structure

The extracellular domain serves as the ligand-binding part of the molecule. It can be a separate unit that is attached to the rest of the receptor by a disulfide bond. The same mechanism can be used to bind two receptors together to form a homo- or heterodimer. The transmembrane element is a single α helix. The intracellular or cytoplasmic domain is responsible for the (highly conserved) **kinase** activity, as well as several regulatory functions.

Regulation

Ligand binding causes two reactions:

1. Dimerization of two monomeric receptor kinases or stabilization of a loose dimer. Many ligands of receptor tyrosine kinases are multivalent. Some tyrosine receptor kinases (e.g., the platelet-derived growth factor receptor) can form heterodimers with other similar but not identical kinases of the same subfamily, allowing a highly varied response to the extracellular signal.
2. *Trans*-autophosphorylation (phosphorylation by the other **kinase** in the dimer) of the **kinase**.

The autophosphorylation causes the two subdomains of the intrinsic **kinase** to shift, opening the **kinase** domain for ATP binding. In the inactive form, the **kinase** subdomains are aligned so that ATP cannot reach the catalytic center of the **kinase**. When several amino acids suitable for phosphorylation are present in the **kinase** domain (e.g., the insulin-like growth factor receptor), the activity of the **kinase** can increase with the number of phosphorylated amino acids; in this case, the first phosphorylation is said to be a *cis*-autophosphorylation, switching the **kinase** from "off" to "standby".

Signal transduction

The active tyrosine **kinase** phosphorylates specific target proteins, which are often enzymes themselves. An important target is the ras **protein** signal-transduction chain.

Receptor-associated tyrosine kinases

Tyrosine kinases recruited to a receptor following hormone binding are receptor-associated tyrosine kinases and are involved in a number of signalling cascades, principally those involved in cytokine signalling (but also others, including growth hormone). One such receptor-associated tyrosine **kinase** is Janus **kinase** (JAK), many of whose effects are mediated by STAT proteins. (*See JAK-STAT pathway.*)

Histidine-specific protein kinases

Histidine kinases are structurally distinct from most other **protein** kinases and are found mostly in prokaryotes as part of two-component signal transduction mechanisms. A phosphate group from ATP is first added to a histidine residue within the **kinase**, and later transferred to an aspartate residue on a 'receiver domain' on a different **protein**, or sometimes on the **kinase** itself. The aspartyl phosphate residue is then active in signaling.

Histidine kinases are found widely in prokaryotes, as well as in plants and fungi. The pyruvate dehydrogenase family of kinases in animals is structurally related to histidine kinases, but instead phosphorylate serine residues, and probably do not use a phospho-histidine intermediate.

Aspartic acid/glutamic acid-specific protein kinases

Mixed kinases

Some kinases have mixed **kinase** activities. For example, MEK (MAPKK), which is involved in the MAP **kinase** cascade, is a mixed serine/threonine and tyrosine **kinase**.

External links

- The **Protein Kinase** Resource (http://pkr.sdsc.edu/): Curated database of **protein kinase** structures and related data
- **Protein kinase** gene resource (http://www.kinase.com/): Genomic analyses, classification and evolution of **protein** kinases
- Kinase3D: A Database of **Protein Kinase** 3D models provided by GEN2X.com (http://www.gen2x.com/news.html)
- Collection of Ser/Thr/Tyr specific **protein** kinases and similar sequences (http://hodgkin.mbu.iisc.ernet.in/~king/)
- KinMutBase: A registry of disease-causing mutations in **protein kinase** domains (http://bioinf.uta.fi/KinMutBase/)
- Evolution of **protein kinase** signaling from yeast to man (http://kinase.com/evolution/TiBS_Kinase_Evolution.pdf) (pdf)

Cell signaling

Key concepts - Ligand | Receptor | Second messenger | **Protein kinase** | Transcription factor | Cell signaling networks

Pathways - Apoptosis | Ca^{2+} signaling | Cytokine signaling | Hedgehog | Integrin signaling | JAK/STAT | Lipid signaling | MAPK/ERK pathway | mTOR | NF-kB | Notch | p53 | TGFβ | Wnt

Categories: Articles with sections needing expansion | EC 2.7 | **Protein** kinases

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CN 4-(2-Nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine
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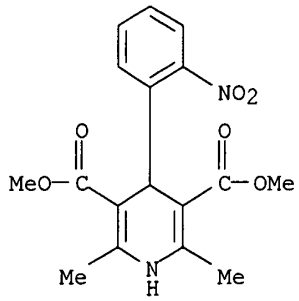

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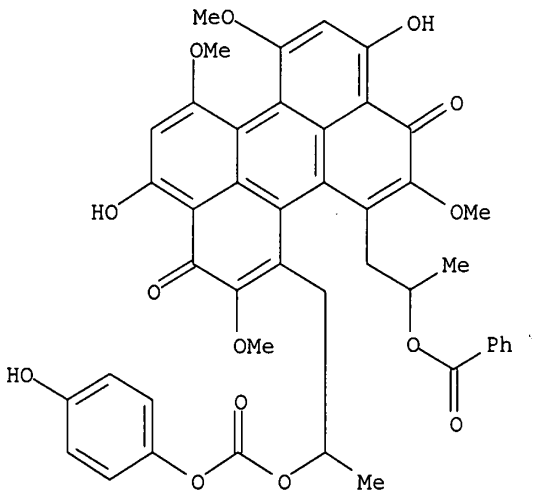
RN 121263-19-2 REGISTRY
ED Entered STN: 23 Jun 1989
CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Perylene, carbonic acid deriv.
OTHER NAMES:
CN **Calphostin C**
CN Cladochrome E
CN PKF 115-584
CN UCN 1028C
DR 125411-36-1
MF C44 H38 O14
SR CA
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, NAPRALERT, PHAR, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

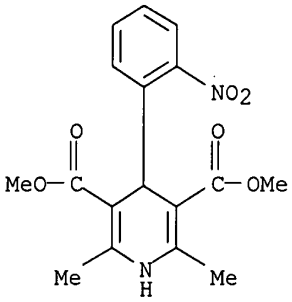
274 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
274 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d l2 30-35

[redacted]

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 21829-25-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-, dimethyl ester (8CI)
OTHER NAMES:
CN 2,6-Dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine
CN 2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester
CN 4-(2-Nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine
CN Adalat
CN Adalat 10
CN Adalat 20
CN Adalat 5
CN Adalat CC
CN Adalat CR
CN Adalat Crono
CN Adalat FT
CN Adalat GITS
CN Adalat GITS 30
CN Adalat LA
CN Adalat LP
CN Adalat Oros
CN Adalat PA
CN Adalat retard
CN Adalate
CN Adapine
CN Adapress
CN Alat
CN Aldipin
CN Alfadat
CN Alonix
CN Alonix S
CN Alpha-Nifedipine Retard
CN Angipec
CN Anifed
CN Anpine
CN Apo-Nifed
CN Aprical
CN BAY 1040
CN BAY-a 1040
CN Bonacid
CN Calcibloc
CN Calcigard
CN Calcilat
CN Camont
CN Cardifen
CN Cardilat
CN Cardilate
CN Cardionorm
CN Chronadalate
CN Chronadalate LP
CN Citilat
CN Coracten
CN Coral
CN Cordafen
CN **Procardia**
CN **Procardia XL**
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for

DISPLAY
FS 3D CONCORD
DR 11104-22-6, 101539-70-2, 101554-38-5
MF C17 H18 N2 O6
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7847 REFERENCES IN FILE CA (1907 TO DATE)
106 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7861 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

=> d ibib abs 1-8 it hitstr

L11 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:49003 CAPLUS
DOCUMENT NUMBER: 142:329754
TITLE: **Nifedipine** protects against overproduction of superoxide anion by monocytes from patients with systemic sclerosis
AUTHOR(S): Allanore, Yannick; Borderie, Didier; Perianin, Axel; Lemarechal, Herve; Ekindjian, Ohvanesse Garabed; Kahan, Andre
CORPORATE SOURCE: Rheumatology A Department, Assistance Publique-Hopitaux de Paris, Paris V University, Cochin Hospital, Paris, Fr.
SOURCE: Arthritis Research & Therapy (2005), 7(1), R93-R100
CODEN: ARTRCV; ISSN: 1478-6362
URL: http://arthritis-research.com/content/pdf/ar1457.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB We have reported previously that dihydropyridine-type calcium-channel antagonists (DTCCA) such as **nifedipine** decrease plasma markers of oxidative stress damage in systemic sclerosis (SScp). To clarify the cellular basis of these beneficial effects, we investigated the effects in vivo and in vitro of **nifedipine** on superoxide anion (O2•-) production by peripheral blood monocytes. We compared 10 healthy controls with 12 patients with SSc, first after interruption of treatment with DTCCA and second after 2 wk of treatment with **nifedipine** (60 mg/day). O2•- production by monocytes stimulated with phorbol myristate acetate (PMA) was quantified by the cytochrome c reduction method. We also investigated the effects in vitro of DTCCA on O2•- production and protein phosphorylation in healthy monocytes and on protein kinase C (PKC) activity using recombinant PKC. After DTCCA had been washed out, monocytes from patients with SSc produced more O2•- than those from controls. **Nifedipine** treatment considerably decreased O2•- production by PMA-stimulated monocytes. Treatment of healthy monocytes with **nifedipine** in vitro inhibited PMA-induced O2•- production and protein phosphorylation in a dose-dependent manner. Finally, **nifedipine** strongly inhibited the activity of recombinant PKC in vitro. Thus, the oxidative stress damage observed in SSc is consistent with O2•- overprodn. by primed monocytes. This was decreased by **nifedipine** treatment both in vivo and in vitro. This beneficial property of **nifedipine** seems to be mediated by its cellular action and by the inhibition of PKC activity. This supports the hypothesis that this drug could be useful for the treatment of diseases associated with oxidative stress.

IT Respiration, animal
(burst; **nifedipine** dose dependently inhibited fMLP-induced monocyte respiratory burst in systemic sclerosis patients)

IT Calcium channel blockers
Human
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

IT Antioxidants
(**nifedipine** had anti-oxidant effect by inhibiting PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of systemic sclerosis patients)

IT Connective tissue, disease
(**nifedipine** inhibited PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of patients with

systemic sclerosis)

IT Monocyte
(**nifedipine** inhibited PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of systemic sclerosis patients)

IT Connective tissue, disease
(scleroderma; **nifedipine** inhibited PKC and PMA induced over production of super oxide anion in peripheral blood monocytes of patients with systemic sclerosis)

IT 55985-32-5, Nicardipine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(calcium channel blockers **nifedipine** and nicardipine had similar inhibitory effect on superoxide anion production from monocytes of healthy humans)

IT **121263-19-2**, Calphostin C 133052-90-1, GF109203x
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

IT **21829-25-4, Nifedipine**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

IT 7722-84-1, Hydrogen peroxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nifedipine** dose dependently inhibited fMLP-induced hydrogen peroxide production from healthy monocytes)

IT 11062-77-4, Superoxide anion
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nifedipine** dose dependently inhibited phorbol myristate acetate-induced monocyte superoxide anion production in systemic sclerosis patients and healthy humans)

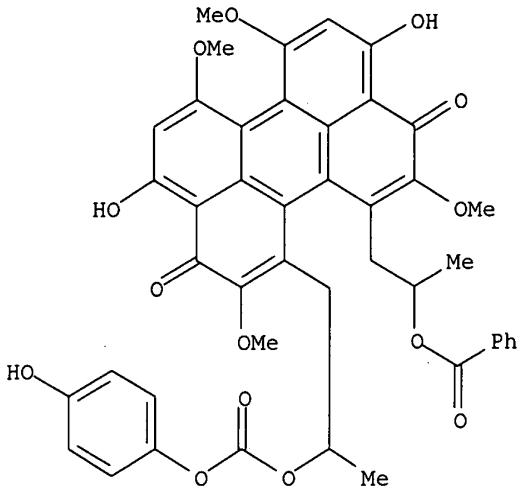
IT 141436-78-4, Protein kinase C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nifedipine** dose dependently inhibited protein kinase C-dependent monocyte protein phosphorylation in vitro and in vivo from patient with systemic sclerosis)

IT 42399-41-7, Diltiazem
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**nifedipine** had high inhibitory effect on superoxide anion production from monocytes of healthy humans than calcium channel blocker diltiazem)

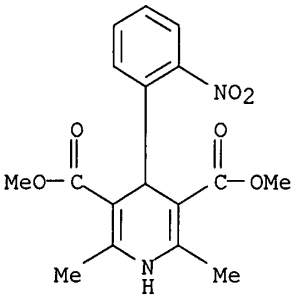
IT **121263-19-2**, Calphostin C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)

RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



IT **21829-25-4, Nifedipine**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dihydropyridine-type calcium-channel antagonist **nifedipine** inhibited PKC and PMA induced over production of super oxide anion and protein phosphorylation in peripheral blood monocytes of systemic sclerosis patients)
RN 21829-25-4 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:157149 CAPLUS
DOCUMENT NUMBER: 145:180830
TITLE: Effects of emodin on Ca2+ signal transduction of smooth muscle cells in multiple organ dysfunction syndrome
AUTHOR(S): Chen, Zheyu; Qinghui, Q. I.; Liu, Lixin; Tao, M. A.; Xu, Jian; Zhang, Liang; Yan, Lunan
CORPORATE SOURCE: Department of General Surgery of West China Hospital, Sichuan University, Chengdu, Peop. Rep. China
SOURCE: Journal of Surgical Research (2006), 131(1), 80-85
CODEN: JSGRA2; ISSN: 0022-4804
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have made several reports on the signal transduction mechanism that emodin enhance the calcium concns. of smooth muscle cells (SMCs) in the physiol. condition by inositol [1,4,5]-friphosphate (IP3). The observation that IP3 concns. in SMCs were decreased in multiple organ dysfunction syndrome (MODS) prompted us to ask whether emodin can activate SMCs to contract by way of elevating [Ca2+] and thus modulating the critical Ca2+ signal transduction pathways involved in the contraction of the SMCs in the pathol. setting of MODS. To test this hypothesis, we used the rat model of MODS to explore the potential roles of emodin in Ca2+ signal transduction in the SMCs of colon in rats. ML-7 [an inhibitor of myosin light-chain kinase (MLCK)] and Calphostin C [an inhibitor of protein kinase C (PKC)] were used to observe the influence of emodin on the muscle strips and SMCs in rats after MODS. **Nifedipine** (an antagonist of voltage-gated Ca2+ channel), EGTA (removal of extracellular Ca2+), heparin (a specific IP3 receptor antagonist), and ryanodine were used to probe the potential mechanisms involved in emodin-mediated elevation of the global cytoplasmic Ca2+ in SMCs of colon in the rats after MODS. Our results show that emodin is capable of contract the smooth muscles of colon in rats after MODS by MLCK increasing [Ca2+] of SMCs, and by PKC enhancing the calcium sensitivity of SMCs. The mechanism by which emodin triggers elevated [Ca2+] of smooth muscles of colon in rats after MODS is likely to operate through IP3 and RyR receptors in the sarcoplasm. It is hoped that deeper insights into how emodin modulates the critical calcium signaling in SMCs might lead to the potential development of emodin in the treatment of MODS.

IT Intestine
(colon; emodin induced colonic smooth muscle contraction by signal path of MLCK increasing [Ca2+] through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT Signal transduction, biological
(emodin contracted colonic smooth muscle by both signal path of MLCK increasing [Ca2+] through IP3 and RyR receptors in sarcoplasm and PKC path enhancing calcium sensitivity in multiple organ dysfunction syndrome rat model)

IT Multiple organ failure
Muscle contraction
(emodin induced colonic smooth muscle contraction by signal path of MLCK increasing [Ca2+] through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT Ryanodine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin induced colonic smooth muscle contraction by signal path of myosin light-chain kinase increasing [Ca2+] through RyR receptor in sarcoplasm of multiple organ dysfunction syndrome rat model)

IT Inositol 1,4,5-trisphosphate receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin induced colonic smooth muscle contraction by signal path of myosin light-chain kinase increasing [Ca2+] through inositol [1, 4, 5]-triphosphate receptor in sarcoplasm of multiple organ dysfunction syndrome rat model)

IT Rheum palmatum
(emodin isolated from Rheum palmatum contracted colonic smooth muscle by MLCK path elevating [Ca2+] via IP3 and RyR receptor in sarcoplasm, by PKC path enhancing calcium sensitivity in SMC of multiple organ dysfunction syndrome rat model)

IT Muscle
(smooth; emodin induced colonic smooth muscle contraction by signal path of MLCK increasing [Ca2+] through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT 518-82-1, Emodin

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anthraquinone derivative emodin contracted colonic smooth muscle by MLCK path increasing [Ca2+] via IP3 and RyR receptor in sarcoplasm and by PKC path enhancing calcium sensitivity in SMC of multiple organ dysfunction syndrome rat model)

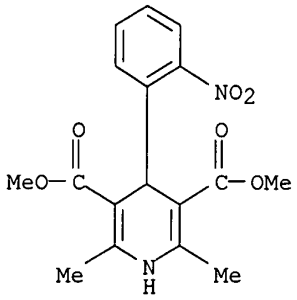
IT 14127-61-8, Calcium ion, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin induced colonic smooth muscle contraction by signal path of MLCK increasing [Ca2+] through IP3 and RyR receptors in sarcoplasm and by PKC path enhancing calcium sensitivity in SMCs of multiple organ dysfunction syndrome rat model)

IT 109376-83-2, ML-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin induced colonic smooth muscle contraction by signal path of myosin light-chain kinase increasing [Ca2+] through inositol [1, 4, 5]-triphosphate and RyR receptors in sarcoplasm of multiple organ dysfunction syndrome rat model)

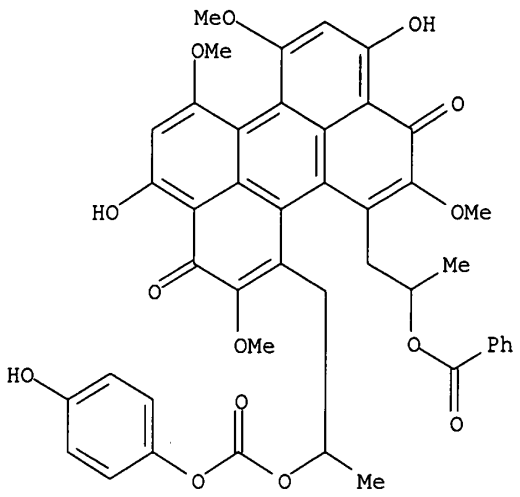
IT 67-42-5, EGTA 9005-49-6, Heparin, biological studies 15662-33-6, Ryanodine **21829-25-4**, **Nifedipine 121263-19-2**, Calphostin c
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin induced colonic smooth muscle contraction by signal path of protein kinase C enhancing calcium sensitivity in smooth muscle cells of multiple organ dysfunction syndrome rat model)

IT **21829-25-4**, **Nifedipine 121263-19-2**, Calphostin c
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin induced colonic smooth muscle contraction by signal path of protein kinase C enhancing calcium sensitivity in smooth muscle cells of multiple organ dysfunction syndrome rat model)

RN 21829-25-4 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS
CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:434972 CAPLUS
DOCUMENT NUMBER: 133:172003
TITLE: Effects of phorbol 12,13-diacetate on human isolated bronchus
AUTHOR(S): Sarria, B.; Pedros, C.; Galan, G.; Cortijo, J.; Morcillo, E. J.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology, University of Valencia, Valencia, E-46010, Spain
SOURCE: European Journal of Pharmacology (2000), 399(1), 65-73
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein kinase C appears to be involved in the regulation of airway contractility. Phorbol 12,13-diacetate (PDA; 0.01-10 μM), a protein kinase C activator, produced a transient relaxation followed by a sustained contraction of human isolated bronchus. Different protein kinase C inhibitors (calphostin C, staurosporine and 1-(5-isoquinolinesulfonyl)-2-methylpiperazine) (H-7), **nifedipine** (NIF; 1 μM) or incubation with Ca2+-free medium, inhibited the spasmogenic response to phorbol, while ouabain (10 μM) suppressed only the initial relaxation. These results indicate that the initial relaxation, in response to PDA, is related to the activation of Na+/K+-ATPase, while the ensuing contraction depends on extracellular Ca2+ entry. Incubation with PDA (1-5 μM) depressed the maximal relaxation to theophylline and caffeine obtained at 37° but augmented the spasmogenic responses to methylxanthines (10 mM) obtained in cooled prepns. These effects do not result apparently from increased extracellular entry of Ca2+, but instead, from facilitation of the release of Ca2+ from intracellular stores.

IT Antiasthmatics
Bronchodilators
(effects of phorbol 12,13-diacetate on human isolated bronchus)

IT 58-08-2, Caffeine, biological studies 58-55-9, Theophylline, biological studies 7683-59-2, Isoprenaline **21829-25-4**, **Nifedipine** 62996-74-1, Staurosporine 84477-87-2 94535-50-9, Levcromakalim **121263-19-2**, Calphostin C
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

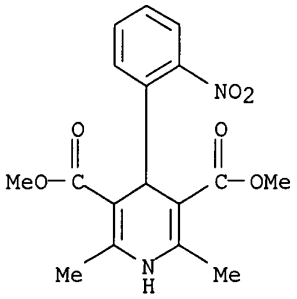
(Uses)
(effects of phorbol 12,13-diacetate on human isolated bronchus)

IT 141436-78-4, Protein kinase C
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of phorbol 12,13-diacetate on human isolated bronchus)

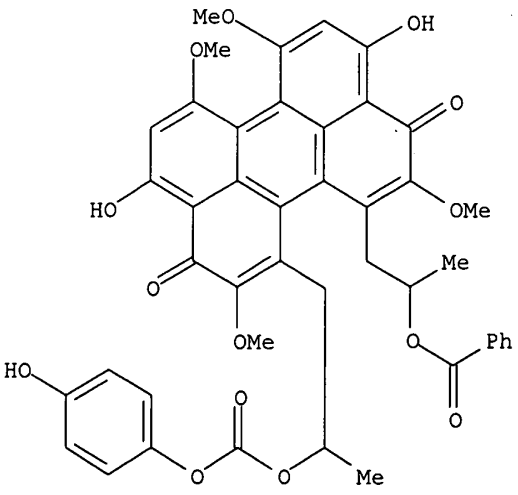
IT 9000-83-3, ATPase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(potassium-sodium-activated; effects of phorbol 12,13-diacetate on human isolated bronchus)

IT **21829-25-4, Nifedipine 121263-19-2,** Calphostin C
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of phorbol 12,13-diacetate on human isolated bronchus)

RN 21829-25-4 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS
CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:100738 CAPLUS
DOCUMENT NUMBER: 144:198849
TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients
INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar
PATENT ASSIGNEE(S): India
SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006024365	A1	20060202	US 2005-134633		20050519
IN 193042	A	20040626	IN 2002-MU697		20020805
US 2004096499	A1	20040520	US 2003-630446		20030729
PRIORITY APPLN. INFO.:			IN 2002-MU697	A	20020805
			IN 2002-MU699	A	20020805
			IN 2003-MU80	A	20030122
			IN 2003-MU82	A	20030122
			US 2003-630446	A2	20030729

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.
IT tRNA

L11 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:373373 CAPLUS
DOCUMENT NUMBER: 141:99005
TITLE: Prediction of P-Glycoprotein Substrates by a Support Vector Machine Approach
AUTHOR(S): Xue, Y.; Yap, C. W.; Sun, L. Z.; Cao, Z. W.; Wang, J. F.; Chen, Y. Z.
CORPORATE SOURCE: Department of Computational Science, Singapore-MIT Alliance, National University of Singapore, 117543, Singapore
SOURCE: Journal of Chemical Information and Computer Sciences (2004), 44(4), 1497-1505
CODEN: JCISD8; ISSN: 0095-2338
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB P-glycoproteins (P-gp) actively transport a wide variety of chems. out of cells and function as drug efflux pumps that mediate multidrug resistance and limit the efficacy of many drugs. Methods for facilitating early elimination of potential P-gp substrates are useful for facilitating new drug discovery. A computational ensemble pharmacophore model has recently been used for the prediction of P-gp substrates with a promising accuracy of 63%. It is desirable to extend the prediction range beyond compds. covered by the known pharmacophore models. For such a purpose, a machine learning method, support vector machine (SVM), was explored for the prediction of P-gp substrates. A set of 201 chemical compds., including 116 substrates and 85 nonsubstrates of P-gp, was used to train and test a SVM classification system. This SVM system gave a prediction accuracy of at least 81.2% for P-gp substrates based on two different evaluation methods, which is substantially improved against that obtained from the multiple-pharmacophore model. The prediction accuracy for nonsubstrates of P-gp is 79.2% using 5-fold cross-validation. These accuracies are slightly better than those obtained from other statistical classification methods, including k-nearest neighbor (k-NN), probabilistic neural networks (PNN), and C4.5 decision tree, that use the same sets of data and mol. descriptors. The study indicates the potential of SVM in facilitating the prediction of P-gp substrates.

IT Biological transport
Molecular modeling
Multidrug resistance
Pharmacophores
Simulation and Modeling
(prediction of P-glycoprotein substrates by support vector machine approach)

IT P-glycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prediction of P-glycoprotein substrates by support vector machine approach)

IT 50-02-2, Dexamethasone 50-06-6, Phenobarbital, biological studies 50-07-7, Mitomycin-C 50-18-0, Cyclophosphamide 50-22-6, Corticosterone 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-27-1, Estriol 50-28-2, Estradiol, biological studies 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 50-55-5, Reserpine 50-76-0, Actinomycin D 51-21-8, Fluorouracil 51-43-4, Epinephrine 52-39-1, Aldosterone 52-53-9, Verapamil 52-86-8, Haloperidol 53-79-2, Puromycin 56-54-2, Quinidine 57-22-7, Vincristine 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-83-0, Progesterone, biological studies 58-32-2, Dipyridamole 58-39-9, Perphenazine 58-40-2, Promazine 58-89-9, Lindane 59-05-2, Methotrexate 60-57-1, Dieldrin 63-25-2, Carbaryl 64-85-7, Deoxycorticosterone 64-86-8, Colchicine 69-23-8, Fluphenazine 71-63-6, Digitoxin 72-43-5, Methoxychlor 72-57-1, Trypan_blue 76-99-3, Methadone 83-43-2,

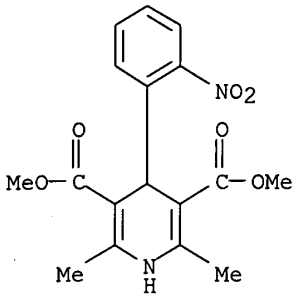
Methylprednisolone 83-60-3, Reserpic_acid 85-79-0, Dibucaine
114-07-8, Erythromycin 115-29-7, Endosulfan 116-06-3, Aldicarb
117-89-5, Trifluoperazine 120-58-1, Isosafrole 130-95-0, Quinine
135-67-1, Phenoxazine 143-62-4, Digitoxigenin 146-48-5, Yohimbine
146-54-3, Triflupromazine 147-94-4, Cytarabine 148-82-3, Melphalan
152-58-9, Cortexolone 154-93-8, Carmustine 305-03-3, Chlorambucil
481-49-2, Cepharanthine 483-18-1, Emetine 485-71-2, Cinchonidine
518-28-5, Podophyllotoxin 569-61-9, Pararosaniline 732-11-6, Phosmet
749-02-0, Spiperone 865-21-4, Vinblastine 1095-90-5, Depridol
1622-62-4, Flunitrazepam 1646-88-4, Aldoxycarb 1672-46-4, Digoxigenin
1912-24-9, Atrazine 1951-25-3, Amiodarone 2001-95-8, Valinomycin
2032-59-9, Aminocarb 2182-14-1, Vindoline 2385-85-5, Mirex
2485-62-3, Cysteine methylester 2901-66-8, Methylreserpate 3690-10-6,
NSC309132 4375-07-9, Epipodophyllotoxin 4602-84-0, Farnesol
4685-14-7, Paraquat 5554-59-6, NSC364080 5602-68-6, NSC49899
7786-34-7, Mevinphos 10311-84-9, Dialifos 10540-29-1, Tamoxifen
13292-46-1, Rifampicin 15639-50-6, Safingol 16662-47-8, Gallopamil
17090-79-8, Monensin 18198-39-5, Tetraphenylphosphonium 18378-89-7,
Mithramycin 19186-35-7, Deoxypodophyllotoxin 19216-56-9, Prazosin
20278-59-5, NSC606532 20290-10-2, Morphine-6-glucuronide 20830-75-5,
Digoxin 20830-81-3, Daunomycin 21609-90-5, Leptophos
21829-25-4, Nifedipine 23214-92-8, Doxorubicin
23491-52-3, HOE33342 23593-75-1, Clotrimazole 25316-40-9, Adriamycin
25953-19-9, Cefazolin 26644-46-2, Triforine 28380-24-7, Nigericin
29767-20-2, Teniposide 33069-62-4, Paclitaxel 33419-42-0, Etoposide
37517-30-9, Acebutolol 42399-41-7, Diltiazem 50471-44-8, Vinclozolin
50679-08-8, Terfenadine 53123-88-9, Rapamycin 53179-11-6, Loperamide
53772-82-0, Cis-Flupenthixol 55985-32-5, Nicardipine 56420-45-2,
Epirubicin 56980-93-9, Celiprolol 57808-66-9, Domperidone
58957-92-9, Idarubicin 59467-70-8, Midazolam 59865-13-3, Cyclosporin A
60207-90-1, Propiconazole 62893-19-0, Cefoperazone 62996-74-1,
Staurosporine 65271-80-9, Mitoxantrone 66085-59-4, Nimodipine
66358-49-4, NSC 314622 67642-36-8, NSC 268251 69712-56-7, Cefotetan
69806-50-4, Fluazifop-butyl 70288-86-7, Ivermectin 73113-90-3,
Hydroxyrubicin 75330-75-5, Lovastatin 75621-03-3, Chaps 75949-61-0,
Pafenolol 78186-34-2, Bisantrene 83799-24-0, Fexofenadine
89778-26-7, Toremifene 90523-31-2, Azidopine 99614-02-5, Ondansetron
114798-26-4, Losartan 114977-28-5, Docetaxel 120054-86-6,
Dexniguldipine **121263-19-2**, Calphostin C 121584-18-7, PSC833
123948-87-8, Topotecan 126463-15-8, NSC623083 127779-20-8, Saquinavir
128666-81-9, NSC686028 131246-38-3, NSC648403 135812-04-3, NSC 615985
137694-16-7, BIBW22 140945-01-3, S9788 142716-85-6, CP100356
143664-11-3, GF120918 150378-17-9, Indinavir 152044-53-6, Epothilone_a
155213-67-5, Ritonavir 159875-50-0, NSC667533 159989-64-7, Nelfinavir
160450-56-6, NSC667532 161976-69-8, NSC666331 167465-36-3, LY335979
182198-53-4, L767679 191729-65-4, NSC678047 200340-45-0, NSC676593
208398-10-1, NSC676610 208398-12-3, NSC676615 208398-21-4, NSC676618
208398-22-5, NSC676617 208398-24-7, NSC676616 432550-02-2, NSC617286
432550-03-3, NSC630148 432550-04-4, NSC630721 432550-05-5, NSC 633528
432550-06-6, NSC664565 432550-08-8, NSC668354 432550-09-9, NSC674508
432550-10-2, NSC 674570 432550-22-6, NSC630357 432550-23-7, NSC639677
432550-24-8, NSC653278 432550-25-9, NSC667551 432550-26-0, NSC667560
432550-27-1, NSC671400 717849-72-4 717849-74-6 718637-11-7, NSC
667558 718637-12-8, NSC 676602
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(prediction of P-glycoprotein substrates by support vector machine
approach)

IT **21829-25-4, Nifedipine 121263-19-2**, Calphostin
C
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(prediction of P-glycoprotein substrates by support vector machine

approach)

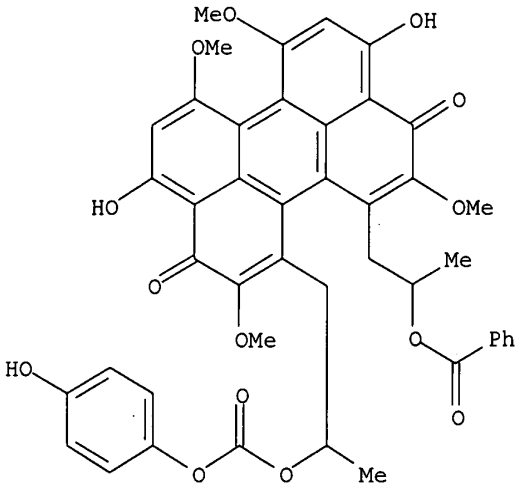
RN 21829-25-4 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:227327 CAPLUS

DOCUMENT NUMBER: 137:148

TITLE: A Computational Ensemble Pharmacophore Model for Identifying Substrates of P-Glycoprotein

AUTHOR(S): Penzotti, Julie E.; Lamb, Michelle L.; Evensen, Erik; Grootenhuis, Peter D. J.

CORPORATE SOURCE: Deltagen Research Laboratories, San Diego, CA, 92121, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(9), 1737-1740
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB P-glycoprotein (P-gp) functions as a drug efflux pump, mediating multidrug resistance and limiting the efficacy of many drugs. Clearly, identification of potential P-gp substrate liability early in the drug discovery process would be advantageous. We describe a multiple-pharmacophore model that can discriminate between substrates and nonsubstrates of P-gp with an accuracy of 63%. The application of this filter allows large virtual libraries to be screened efficiently for compds. less likely to be transported by P-gp.

IT Conformation
Drug screening
Multidrug resistance
Pharmacophores
Simulation and Modeling
(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT P-glycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT Chemistry
(computational; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT Biological transport
(drug; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT Biological transport
(efflux; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

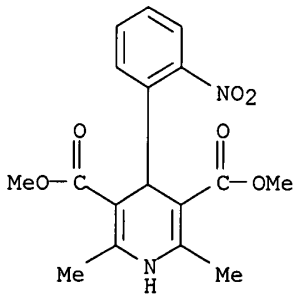
IT 73113-90-3, Hydroxyrubicin
RL: PRP (Properties)
(Hydroxyrubicin; computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT 50-02-2, DEXAMETHASONE 50-06-6, PHENOBARBITAL, properties 50-07-7, MITOMYCIN C 50-18-0, CYCLOPHOSPHAMIDE 50-22-6, CORTICOSTERONE 50-23-7, HYDROCORTISONE 50-24-8, PREDNISOLONE 50-27-1, ESTRIOL 50-52-2, THIORIDAZINE 50-55-5, RESERPINE 50-76-0, Actinomycin D 51-21-8, FLUOROURACIL 51-43-4, EPINEPHRINE 52-39-1, ALDOSTERONE 52-53-9, VERAPAMIL 53-79-2, PUROMYCIN 56-54-2, QUINIDINE 57-22-7, VINCRISTINE 57-41-0, PHENyTOIN 57-83-0, PROGESTERONE, properties 58-39-9, PERPHENAZINE 58-89-9, LINDANE 60-57-1, DIELDRIN 63-25-2, CARBARYL 64-85-7, DEOXYcorticosterone 64-86-8, Colchicine 69-23-8, FLUPHENAZINE 71-63-6, DIGITOXIN 72-43-5, METHOXYCHLOR 72-57-1, TRYPAN BLUE 76-99-3, METHADONE 83-43-2, METHYLPREDNISOLONE 83-60-3, Reserpic acid 85-79-0, DIBUCAINE 114-07-8, ERYTHROMYCiN 115-29-7, ENDOSULFAN* 116-06-3, ALDICARB 117-89-5, TRIFLUOPERAZINE 120-58-1, ISOSAFROLE 130-95-0, QUININE 135-67-1, PHENOXAZINE 143-62-4, DIGITOXIGENIN 146-48-5, YOHIMBINE 146-54-3, TRIFLUPROMAZINE 147-94-4, CYTARABINE 148-82-3, MELPHALAN 152-58-9, CORTEXOLONE 154-93-8, CARMUSTINE 305-03-3, CHLORAMBUCIL 481-49-2, CEPHARANTHINE 485-71-2, CINCHONIDINE 732-11-6, PHOSMET 749-02-0, SPIPERONE 865-21-4, VINBLASTINE 1646-88-4, ALDOXYCARB 1672-46-4, DIGOXIGENIN 1912-24-9, ATRAZINE 1951-25-3, Amiodarone 2001-95-8, Valinomycin 2182-14-1, VINDOLINE 2385-85-5, MIREX 2468-21-5 2709-56-0, FLUPENTHIXOL 2751-90-8, TETRAPHENYL PHOSPHONIUM BROMIDE 2901-66-8, METHYLRESERPATE 3131-03-1, PRISTINAMYCiNIA 3690-10-6, NSC 309132 4375-07-9, EPIPODOPHYLLOTOXI N 4602-84-0, FARNESOL 4685-14-7, PARAQUAT 5554-59-6, NSC 364080 5602-68-6, NSC 49899 7786-34-7, MEVINPHOS 10311-84-9, DIALIFOS 10540-29-1, TAMOXIFEN 13292-46-1, RIFAMPICIN 15639-50-6, SAFINGOL 16662-47-8, GALLOPAMIL 17090-79-8, MONENSIN 18378-89-7, MITHRAMYCIN A 19186-35-7, DEOXY-PODOPHYLLOTOXIN 19216-56-9, PRAZOSIN 20278-59-5, NSC 606532 20290-10-2, MORPHINE 6-GLUCURONIDE 20830-75-5, DIGOXIN 20830-81-3, DAUNORUBICIN 21609-90-5, LEPTOPHOS **21829-25-4, NIFEDIPINE**

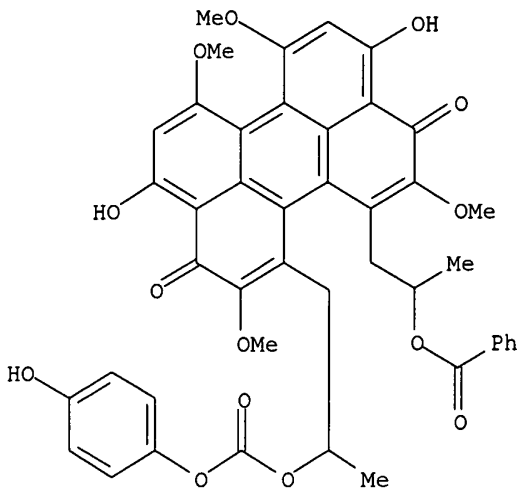
23214-92-8, DOXORUBICiN 23491-52-3, HOE33342 23593-75-1, CLOTRIMAZOLE
25953-19-9, CEFAZOLIN 26644-46-2, TRIFORINE 28380-24-7, Nigericin
29767-20-2, TENIPOSIDE 33069-62-4, PACLITAXEL 33419-42-0, ETOPOSIDE
37517-30-9, ACEBUTOLOL 41575-94-4, CARBOPLATIN 42399-41-7, DILTIAZEM
44641-43-2, CYSTEINE methyl ESTER 50471-44-8, VINCLOZOLIN 50679-08-8,
TERFENADINE 53123-88-9, RAPAMYCIN 53179-11-6, LOPERAMIDE 53772-82-0,
cis-Flupenthixol 55123-66-5, LEUPEPTIN 55985-32-5, NICARDIPINE
56980-93-9, CELIPROLOL 58957-92-9, IDARUBICIN 59467-70-8, MIDAZOLAM
59865-13-3, Cyclosporin A 60207-90-1, PROPICONAZOLE 62669-70-9,
RHODAMINE 123 62893-19-0, CEFOPERAZONE 62996-74-1, STAUROSPORINE
64706-54-3, BEPRiDIL 65271-80-9, MITOXANTRONE 66085-59-4, NIMODIPINE
66358-49-4, NSC 314622 67642-36-8 68000-92-0 69712-56-7, CEFOTETAN
69806-50-4, FLUAZIFOPBUTYL 70288-86-7, IVERMECTIN 75330-75-5,
LOVASTATIN 75621-03-3, CHAPS 75949-61-0, PAFENOLOL 78186-34-2,
BISANTRENE 89778-26-7, TOREMIFENE 90523-31-2, AZIDOPINE 99614-02-5,
ONDANSETRON 114977-28-5, DOCETAXEL 120054-86-6, DEXNIGULDIPINE
120685-11-2, CG P-41251 **121263-19-2**, CALPHOSTIN C 121584-18-7,
SDZ PSC-833 123948-87-8, TOPOTECAN 126463-15-8, NSC 623083
127779-20-8, SAQUINAVIR 128666-81-9, NSC 686028 130062-64-5
131246-38-3, NSC 648403 135812-04-3, NSC 615985 137694-16-7, BIBW 22BS
140945-01-3, S 9788 143664-11-3, GF 120918 150378-17-9, INDINAVIR
152044-53-6, EPOTHILONE A 155252-35-0 155252-36-1 159875-50-0, NSC
667533 159989-64-7, NELFINAVIR 160450-56-6, NSC 667532 161976-69-8,
NSC 666331 164665-13-8 167465-36-3, LY335979 182198-53-4, L-767679
191729-65-4, NSC 678047 200340-45-0, NSC 676593 208398-10-1, NSC
676610 208398-12-3, NSC 676615 208398-21-4, NSC 676618 208398-22-5,
NSC 676617 208398-24-7, NSC 676616 210365-50-7 210365-51-8
210365-55-2 210365-56-3 211060-81-0 432041-70-8 432550-02-2, NSC
617286 432550-03-3, NSC 630148 432550-04-4, NSC 630721 432550-05-5
432550-06-6, NSC 664565 432550-08-8, NSC 668354 432550-09-9, NSC
674508 432550-10-2 432550-22-6, NSC 630357 432550-23-7, NSC 639677
432550-24-8, NSC 653278 432550-25-9, NSC 667551 432550-26-0, NSC
667560 432550-27-1, NSC 671400
RL: PRP (Properties)
(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

IT **21829-25-4**, **NIFEDIPINE** **121263-19-2**, CALPHOSTIN C
RL: PRP (Properties)
(computational ensemble pharmacophore model for identifying substrates of P-glycoprotein)

RN 21829-25-4 CAPLUS
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS
CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:132450 CAPLUS
DOCUMENT NUMBER: 128:252560
TITLE: Internalization of Aeromonas hydrophila by fish epithelial cells can be inhibited with a tyrosine kinase inhibitor
AUTHOR(S): Tan, E.; Low, K. W.; Wong, W. S. F.; Leung, K. Y.
CORPORATE SOURCE: School of Biological Sciences, Faculty of Science, National University of Singapore, Singapore, 119260, Singapore
SOURCE: Microbiology (Reading, United Kingdom) (1998), 144(2), 299-307
CODEN: MROBEO; ISSN: 1350-0872
PUBLISHER: Society for General Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aeromonas hydrophila is a Gram-neg. bacterium that is pathogenic in fish by causing motile aeromonadic septicemia. It can enter (invade) fish cells and survive as an intracellular parasite. The host-pathogen interaction and signal transduction pathway were studied by screening signal transduction inhibitors using carp epithelioma papillosum cells (EPC) and a virulent strain of the bacterium, PPD134/91. Genistein, a tyrosine kinase inhibitor, delayed the internalization of A. hydrophila into host cells, suggesting that tyrosine phosphorylation plays a role in the internalization process. Staurosporine, a protein kinase C inhibitor, and sodium orthovanadate, a protein tyrosine phosphatase inhibitor, accelerated the internalization. Other virulent strains of A. hydrophila were also examined It is likely that all strains, irresp. of their serogroups, use the same signalling pathway to facilitate the bacterial uptake by cells.

IT Actins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(F-; genistein effects on Aeromonas hydrophila internalization by fish epithelial cells)

IT Aeromonas hydrophila
Epithelium
(genistein effects on Aeromonas hydrophila internalization by fish

epithelial cells)

IT Biological transport
(internalization; genistein effects on Aeromonas hydrophila internalization by fish epithelial cells)

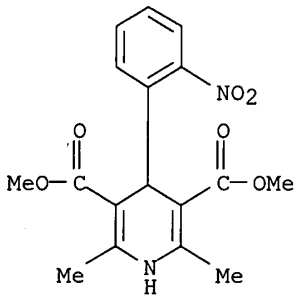
IT Cytotoxic agents
(tyrphostins; genistein effects on Aeromonas hydrophila internalization by fish epithelial cells)

IT 152-11-4, Verapamil hydrochloride 446-72-0, Genistein 486-66-8, Daidzein 13721-39-6, Sodium orthovanadate **21829-25-4**, **Nifedipine** 62996-74-1, Staurosporine 70563-58-5, Herbimycin a 78111-17-8, Okadaic acid 101932-71-2, Calyculin a 118409-60-2, Tyrphostin 47 **121263-19-2**, Calphostin c
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(genistein effects on Aeromonas hydrophila internalization by fish epithelial cells)

IT **21829-25-4**, **Nifedipine** **121263-19-2**, Calphostin c
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(genistein effects on Aeromonas hydrophila internalization by fish epithelial cells)

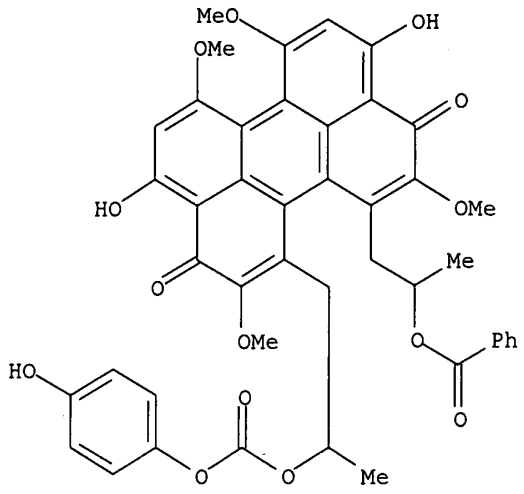
RN 21829-25-4 CAPLUS

CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:113253 CAPLUS
DOCUMENT NUMBER: 142:309808
TITLE: Effect of emodin on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome
AUTHOR(S): Chen, Zhe-yu; Qi, Qing-hui; Ma, Tao; Jian, Xu
CORPORATE SOURCE: The West China Hospital, Sichuan University, Chengdu, 610041, Peop. Rep. China
SOURCE: Zhongguo Zhongxiyi Jiehe Zazhi (2004), 24(12), 1106-1109
CODEN: ZZJZAS; ISSN: 1003-5370
PUBLISHER: Zhongguo Zhongxiyi Jiehe Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Objective: To observe the effect of emodin on motility signal transduction and calcium ion in colonic smooth muscle cells (SMC) in rats with bacterial peritonitis caused multiple organ dysfunction syndrome (MODS). Methods: Observation was conducted in colon of MODS model rats on (1) effects of emodin on the contraction of muscular strip and cells of colonic smooth muscle, and influences of specific myoglobulin light chain kinase inhibitor (ML-7) and selective protein kinase C inhibitor (Calphostin C) on these effects; and (2) effect of emodin on calcium ion in SMC. Results: Emodin could directly contract the muscular strip and cells of smooth muscle; ML-7 and Calphostin could inhibit these contractile action to some extent. Under MODS condition, emodin could still increase the intracellular calcium ion concentration; this effect could be inhibited by heparin (inosamine triphosphate receptor inhibitor) IP3 and ryanodine receptor inhibitor in MODS model but the calcium chelator EGTA and **nifedipine** (the specific cell membrane voltage dependent calcium channel blocker) showed no influence on it. Conclusion: Emodin could directly contract the colonic smooth muscle in MODS model rats, which is mediated by raise the signal path MLCK of calcium ion and the PKCα path for increase calcium sensibility. The mechanism of increasing calcium ion is mainly through IP3 and RyR the two calcium ion channel receptor in the sarcoplasm.

IT Intestine
(colon; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Cell migration
(colonic smooth muscle; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Multiple organ failure
Signal transduction, biological
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Calcium channel
Inositol 1,4,5-trisphosphate receptors
Ryanodine receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Inflammation
Peritoneum, disease
(peritonitis, bacterial; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT Cytoplasm
(sarcoplasm; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

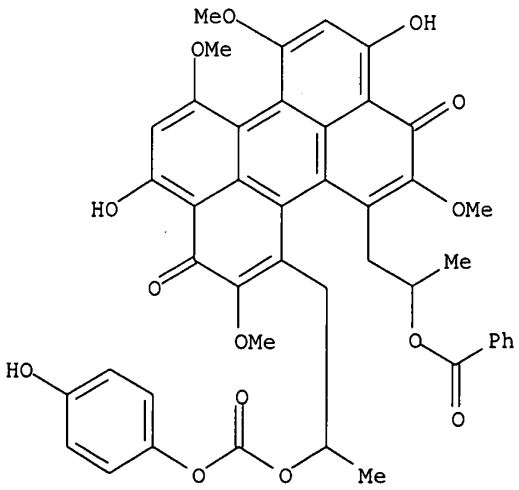
IT Muscle
(smooth; emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT 14127-61-8, Calcium ion, biological studies 109376-83-2, ML-7
121263-19-2, Calphostin C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

IT **121263-19-2**, Calphostin C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(emodin effect on motility signal transduction in colonic smooth muscle cells in rats with multiple organ dysfunction syndrome)

RN 121263-19-2 CAPLUS

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



=> SET TERMSET E#

SET COMMAND COMPLETED

=> DEL SEL Y

=> SEL L1 1 RN

E1 THROUGH E1 ASSIGNED

=> S E1/RN

L3 1 121263-19-2/RN

=> SET TERMSET LOGIN

SET COMMAND COMPLETED

=> FIL NAPRALERT

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.52	29.80

FILE 'NAPRALERT' ENTERED AT 12:52:22 ON 28 AUG 2006
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FILE COVERS 1650 TO 8 AUG 2005 (20050808/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

****** The NAPRALERT File is no longer being updated. ******

=> S L3

L4 5 L3

=> file caplus biosis embase

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.73	30.53

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=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.76	33.29

[redacted]

FILE 'REGISTRY' ENTERED AT 12:53:47 ON 28 AUG 2006

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 AUG 2006 HIGHEST RN 904741-41-9
DICTIONARY FILE UPDATES: 27 AUG 2006 HIGHEST RN 904741-41-9

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REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s procardia
L5 1 PROCARDIA

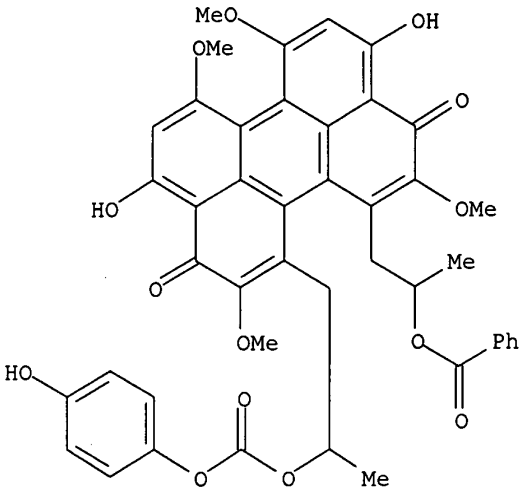
=> d

L15 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:124725 CAPLUS
DOCUMENT NUMBER: 140:178861
TITLE: Calphostin-C Induction of Vascular Smooth Muscle Cell Apoptosis Proceeds through Phospholipase D and Microtubule Inhibition
AUTHOR(S): Zheng, Xi-Long; Gui, Yu; Du, Guangwei; Frohman, Michael A.; Peng, Dao-Quan
CORPORATE SOURCE: Department of Biochemistry & Molecular Biology, Smooth Muscle Research Group, University of Calgary, Calgary, AB, T2N 4N1, Can.
SOURCE: Journal of Biological Chemistry (2004), 279(8), 7112-7118
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Calphostin-C, a protein kinase C inhibitor, induces apoptosis of cultured vascular smooth muscle cells. However, the mechanisms are not completely defined. Because apoptosis of vascular smooth muscle cells is critical in several proliferating vascular diseases such as atherosclerosis and restenosis after **angioplasty**, we decided to investigate the mechanisms underlying the calphostin-C-induced apoptotic pathway. We show here that apoptosis is inhibited by the addition of exogenous phosphatidic acid, a metabolite of phospholipase D (PLD), and that calphostin-C inhibits completely the activities of both isoforms of PLD, PLD1 and PLD2. Overexpression of either PLD1 or PLD2 prevented the vascular smooth muscle cell apoptosis induced by serum withdrawal but not the calphostin-C-elicited apoptosis. These data suggest that PLDs have anti-apoptotic effects and that complete inhibition of PLD activity by calphostin-C induces smooth muscle cell apoptosis. We also report that calphostin-C induced microtubule disruption and that the addition of exogenous phosphatidic acid inhibits calphostin-C effects on microtubules, suggesting a role for PLD in stabilizing the microtubule network. Overexpressing PLD2 in Chinese hamster ovary cells phenocopies this result, providing strong support for the hypothesis. Finally, taxol, a microtubule stabilizer, not only inhibited the calphostin-C-induced microtubule disruption but also inhibited apoptosis. We therefore conclude that calphostin-C induces apoptosis of cultured vascular smooth muscle cells through inhibiting PLD activity and subsequent microtubule polymerization

IT **121263-19-2**, Calphostin-C
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(calphostin-C induction of vascular smooth muscle cell apoptosis proceeds through phospholipase D and microtubule inhibition)

RN 121263-19-2 CAPLUS
CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 2 USPATFULL on STN

ACCESSION NUMBER:	2002:262057 USPATFULL			
TITLE:	Agents for the prevention of damages caused by stress conditions			
INVENTOR(S):	Bar-Shavit, Rachel, Jerusalem, ISRAEL			
PATENT ASSIGNEE(S):	Hadasit Medical Research Services & Development Limited, Jerusalem, ISRAEL (non-U.S. corporation)			

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6461611	B1	20021008	
	WO 9942483		19990826	
APPLICATION INFO.:	US 2000-600031		20000720	(9)
	WO 1999-IL95		19990216	
			20000720	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-123349	19980218

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Tate, Christopher R.
ASSISTANT EXAMINER:	Winston, Randall
LEGAL REPRESENTATIVE:	Oliff & Berridge, PLC
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT:	634

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical compositions for the treatment of a decrease in the levels of protease activated receptor (PAR) mRNA caused by a lack or decrease of oxygen level and/or a lack or decrease of blood flow including pharmaceutically acceptable carriers and activators of PAR are provided. Methods for prevention of a decrease in the levels of protease-activated receptor PAR mRNA caused by lack or decrease in the oxygen level and/or lack or decrease in blood flow are also provided.

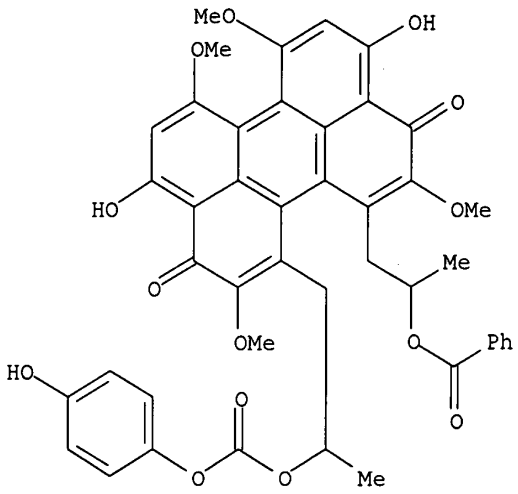
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **121263-19-2**, Calphostin C
(protease-activated receptor (PAR) activators for prevention of damage

caused by stress conditions such as hypoxia or ischemia)

RN 121263-19-2 USPATFULL

CN Carbonic acid, (1R)-2-[12-[(2R)-2-(benzoyloxy)propyl]-3,10-dihydro-4,9-dihydroxy-2,6,7,11-tetramethoxy-3,10-dioxo-1-perylenyl]-1-methylethyl 4-hydroxyphenyl ester, stereoisomer (9CI) (CA INDEX NAME)



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